equations

- **Clearance for low Extraction Ratio(ER) drugs:**

$Cl = F_u * Cl_{int}$

F_u↑ (fraction unbound to plasma proteins) is affected by drug displacement ↑.

Cl_{int} is decreased by enzyme inhibition & increased by enzyme induction

- **Clearance for high Extraction Ratio(ER) drugs:**

$Cl = Q_H$ (hepatic blood flow)

- **Another general equations (تجميعة للقوانين المستخدمة):**

$Cl = K * V$

$K = 0.693 / t_{1/2}$

$V = V_p + V_T*(F_u/F_{uT})$

$\frac{dose}{t} = Cl * CP^{ss}$ → t (tau) dose interval

$f_{(bio\ availability)} * \frac{dose}{t} = Cl * CP^{ss}$ (for a drug administered orally)

$CP^{SS} = Cu^{SS} / f_u$

Q 1 (page 13) :

Predict the changes in the elimination half lives for drugs characterized by low & high extraction ratios as a result of an increase in the fraction unbound to plasma proteins(f_U) & tissue proteins (f_{ut}).

(الحل هيبقى متقسم على أربع مراحل .. مرحلة لكل حالة)

1) **for LOW Extraction Ratio(ER) drugs & increase in (F_u) :**

$Cl = K\ V$, $K = 0.693/t_{1/2}$

So:

$F_u * Cl_{int} = 0.693/t_{1/2} * V$ ----------> (1)

This is a relationship between $t_{1/2}$ & F_u , But we should know first whether (V) value will be affected by increase in (F_u) or not … to know that we should apply an equation in which (V) & (F_u) values are involved .

This is the equation:

$V = V_p + V_T * F_u/F_{uT}$ ----------> (2)

from (2)

when (F_u) ↑ …… (V) will ↑

So:

F_u↑ * $Cl_{int} = 0.693/t_{1/2} * V$ ↑

i.e $t_{1/2}$ won't be changed (↔) (because both V & Fu increased & each of them will counter the effect of other)

2) For LOW Extraction Ratio(ER) drugs & increase in (F_{uT}):

$Cl = K V$, $K = 0.693/t_{1/2}$

So:

$F_u * Cl_{int} = 0.693/t_{1/2} * V$ ----------> (1)

$V = V_p + V_T * F_u/F_{uT}$ ----------> (2)

when (F_{uT}) ↑ …… (V) will ↓

so

$F_u * Cl_{int} = 0.693/t_{1/2} * V$ ----------> (1)

when (V) ↓ …… ($t_{1/2}$) will ↓

i.e $t_{1/2}$ will decrease ↓

3) For HIGH Extraction Ratio(ER) drugs & increase in (F_u) :

$Cl = K\ V$, $K = 0.693/t_{1/2}$

So:

$Q_H = 0.693/t_{1/2} * V$ ----------> (1)

$V = V_p + V_T * F_u/F_{uT}$ ----------> (2)

from (2)

when (F_u) ↑ ..... (V) will ↑

From equation (1) , when (V) ↑ , what will happen to ($t_{1/2}$) ???

(N.B hepatic blood flow Q_H is const.)

Right.. ($t_{1/2}$) will increase :D

4) For HIGH Extraction Ratio(ER) drugs & increase in (F_{uT}) :

$Cl = K\ V$, $K = 0.693/t_{1/2}$

So:

$Q_H = 0.693/t_{1/2} * V$ ----------> (1)

$V = V_p + V_T * F_u/F_{uT}$ ----------> (2)

from (2)

when (F_{uT}) ↑ …… (V) will ↓

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from equation (1) , when (V) ↓ , what will happen to ($t_{1/2}$) ???

(N.B hepatic blood flow Q_H is const.)

($t_{1/2}$) will decrease.

Q 2 (page 15)

Question:

Explain (using equations) the above mechanism of the effect of valproic acid (displacement from protein binding sites and inhibition of metabolism) on phenytoin plasma levels (total and free concentrations).

Displacement → F_u↑

Inhibition of metabolism → Cl_{int}↓

We should know (from lec.) that Phenytoin is <u>low ER drug.</u>

(dr.yousry said that u should memorize these examples & mechanisms of action (Page.14,15) from the drug-drug interaction lecture)

$$1-\frac{dose}{t} = Cl * CP^{ss}$$

(CP^{ss} is the <u>total conc.</u> Of phenytoin in plasma)

$$\frac{dose}{t} = F_u \uparrow * Cl_{int} \downarrow * CP^{ss}$$

So CP^{ss} won't change ↔

2- $f_u = Cu^{ss}/cp^{ss}$ →→→ $cp^{ss} = Cu^{ss}/ f_u$

$$\frac{dose}{t} = F_u * Cl_{int} * Cu^{ss}/ f_u$$

$$\frac{dose}{t} = -Cl_{int} \downarrow * Cu^{ss} \uparrow$$

So Cu^{ss} will increase.

Q 3 (page 20)

Question

Predict the effect of enzyme induction or inhibition on the average total and free steady-state plasma concentrations for orally administered high extraction ratio drugs.

20

the drug is administered orally so equation used will be :

$$f_{(\text{bio availability})} * \frac{\text{dose}}{t} = Cl * CP^{ss}$$

for high ER drugs

- $f = Q_H / (f_u.cl_{int})$
- $Cl = Q_H$

$$\cancel{Q_H} / (f_u.cl_{int}) * \frac{\text{dose}}{t} = \cancel{Q_H} * CP^{ss}$$

$$1 / (f_u.cl_{int}) * \frac{\text{dose}}{t} = CP^{ss}$$

First in case of enzyme inhibition :

$$1 / (f_u . cl_{int} \downarrow) \quad * \quad \frac{dose}{t} = CP^{ss} \uparrow$$

i.e total Steady State plasma conc. ↑

$$f_u = Cu^{ss}/CP^{ss} \quad \rightarrow \quad CP^{ss} = Cu^{ss} / f_u$$

$$1 / (f_u . cl_{int}) \quad * \quad \frac{dose}{t} = Cu^{ss} / f_u$$

$$1 / (cl_{int} \downarrow) \quad * \quad \frac{dose}{t} = Cu^{ss} \uparrow$$

i.e Free SS plasma conc. ↑

second in case of enzyme induction :

$$1 / (f_u . cl_{int} \uparrow) \quad * \quad \frac{dose}{t} = CP^{ss} \downarrow$$

i.e total Steady State plasma conc. ↓

$$f_u = Cu^{ss}/CP^{ss} \quad \rightarrow \quad CP^{ss} = Cu^{ss} / f_u$$

$$1 / (f_u . cl_{int}) \quad * \quad \frac{dose}{t} = Cu^{ss} / f_u$$

$$1 / (cl_{int} \uparrow) \quad * \quad \frac{dose}{t} = Cu^{ss} \downarrow$$

i.e Free SS plasma conc. ↓

Q 4 (page 21)

Question:

Predict the changes in the elimination half lives for drugs characterized by low and high extraction ratios as a result of enzyme induction or inhibition.

1- In case of (Low ER ratio drugs & enzyme Inhibition)

$Cl = K\,V$, $K = 0.693/t_{1/2}$

i.e $F_u * Cl_{int} = 0.693/t_{1/2} * V$

فاكرين في المسئلة الأولى عملنا إيه بعد كدة ؟
إستخدمنا القانون ده

$$V = V_p + V_T * F_u/F_{uT}$$

علشان نعرف الـ V نظامها إيه .. هتزيد ولا هتقل ..

بس في المسئلة اللي في ايدينا دي مش هنستخدم هذا القانون ... ليه ؟

علشان أصلا هو ماقلش في البروبلم حاجة عن الـ Fu وبالتالي هي مش هتأثر على الـ V وبالتالي هي ثابتة

يبقى نعمل الأسهم بتاعتنا ونحدد الإجابة على طول

i.e $F_u * Cl_{int} \downarrow = 0.693/t_{1/2} \uparrow * V$

i.e $t_{1/2} \uparrow$

2- In case of (Low ER ratio drugs & enzyme Induction)

$Cl = K\,V$, $K = 0.693/t_{1/2}$

i.e $F_u * Cl_{int} \uparrow = 0.693/t_{1/2} \downarrow * V$

i.e $t_{1/2} \downarrow$

3- In case of (High ER ratio drugs & enzyme inhibition)

$Cl = Q_H$

Q_H = ($0.693/t_{1/2}$) . V

Is there a relationship between $t_{1/2}$ & Cl_{int} ?

in this case; of course not ☺

so $t_{1/2}$ will be …… ↔

4- In case of (High ER ratio drugs & enzyme induction)

زي اللي فاتت بالظبط...

Question no. 5

سؤال أخير الدكتور ملاه في المحاضرة بتاعة الـ drug drug interactions وهو :

الـ digoxin بيزود الـ F_{UT}↑ بتاعة الـ quindine

وكمان بيقلل الـ active secretion يعني (Cl_{int} ↓)

السؤال .. ليه الـ $t_{1/2}$ للـ quinidine مش بتتأثر ؟؟؟

الحل :

- 1st effect of F_{UT}↑ on (V)

$V↓ = V_p + V_T * F_u / F_{UT}↑$

- Active secretion ↓ $\overset{i.e}{\rightarrow}$ $\overset{i.e}{}$ Cl_{int} ↓

$Cl = K V$, $K = 0.693/t_{1/2}$

From the eq. $F_u * Cl_{int}↓ = 0.693/t_{1/2} * V↓$

So $t_{1/2}$ remains without change .. ↔

ماتنسوش الصدقة الجارية يوم الكلينيكال بإذن الله ☺